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The Effects of HIV on P300 are Moderated by Familial Risk for Substance Dependence: Implications for a Theory of Brain Reserve

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Abstract

Background—The goal of the study was to test the validity of additive versus synergistic versus underadditive versions of brain reserve theory within the context of HIV/AIDS. In addition, it tested the convergent validity of 2 operational definitions of premorbid reserve: verbal IQ (VIQ) and a family history (FH) of substance abuse or dependence.

Methods—Seventy HIV-1 seronegative and 115 HIV-1 seropositive male and female volunteers were assigned to 4 subgroups defined by the crossing of a VIQ score < versus ≥ 90 with the presence versus absence of a paternal history of alcohol, cocaine, or opiate abuse or dependence. The principal dependent measure was the P300 event related brain potential elicited during the Stroop color-word interference task.

Results—The principal finding was an underadditive effect of FH plus HIV/AIDS on P300 area over the frontal region: FH reduced frontal scalp P300 to such a degree that the additional effects of HIV/AIDS were blunted. The alternate operational definition of brain reserve, VIQ, had no effect on P300 and did not alter the effects of HIV/AIDS.

Conclusions—Familial risk for substance dependence and low VIQ compromise different aspects of brain structure and/or function and therefore differ in their relationship to HIV/AIDS and P300. Genetic differences associated with familial risk may reduce brain reserve to such a degree that the neurophysiological effects of HIV/AIDS can no longer be measured.

Keywords

HIV-1; Family History; P300; IQ; event related potentials

1. Introduction

The rationale for the present study derives from a neuropsychological theory of brain reserve (BR). BR theory views premorbid variables, such as VIQ, educational attainment, or brain size, as important factors explaining the wide variation in functional outcomes after brain disease or injury across patients with similar structural deficits. It has been invoked by investigators studying HIV/AIDS (Stern et al., 1996; Tomasi et al., 2006), dementia (Spitznagel and

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Tremont, 2005; Zhang et al., 1990), Alzheimer's Disease (Bennett et al., 2003; Scarmeas et al., 2004; Stern et al., 1994), multiple sclerosis (Cader et al., 2006), and other disorders (Farmer et al., 2002; Kesler et al., 2003; Ropacki et al., 2003), as well as normal aging (Stern et al., 2004).

Since 1988 (Katzman et al., 1988), several versions of BR theory have been proposed. According to one version, better premorbid function (i.e., a higher level of brain reserve) is viewed as protective against the effects of neuropsychiatric disease because the premorbid level is more distant from the threshold for clinical impairment, and the new level of functioning attained after disease onset is therefore less likely to cross the threshold. This version has been characterized as passive (Satz et al., 1993). It views the disease or injury as subtracting capacity from the premorbid reserve but does not recognize a role for the brain in actively compensating for the loss. The top panel in Figure 1 illustrates this theory applied to hypothetical data from a forced-choice task in which 50% correct represents the measurement floor (i.e., a chance level of accuracy).

A second version of BR theory is described as active. In this version, high levels of reserve are hypothesized to antagonize the adverse effects of neuropsychiatric disease (Pereda et al., 2000; Staff et al., 2004; Stern, 2002). In contrast, low levels amplify adverse effects. The proposal has a simplistic and intuitive appeal--a larger or more synaptically complex brain (Katzman et al., 1988; Mori et al., 1997; Wallace et al., 1992) should be more successful in compensating for the effects of disease by relying upon its larger reserve of existing resources and recruiting alternative strategies and circuits. However, a brain already compromised in its size or function, as a result of a genetic or environmental deficit, should be less successful. The middle panel of Figure 1 illustrates this theoretical model.

A third version of brain reserve theory is shown in the bottom panel of Figure 1. It assumes a more powerful effect of reduced premorbid reserve on brain function. As a result, the level of function approaches the minimum, and the disease can have no further detrimental effect. Unlike other versions, this version of BR theory proposes that the strength of the correlation (i.e., neuroanatomical overlap) between the measures of premorbid reserve and outcome is critical in determining whether patients with greater premorbid reserve will be more versus less impaired following disease onset.

The present study is significant for it tests the relative validity of these three alternate versions of BR theory within the context of HIV/AIDS. It was hypothesized that the nature of the relationship between premorbid reserve and HIV/AIDS would vary as a function of how premorbid reserve was defined and of the association between the definition and outcome variable. Dependence on a specific operational definition of reserve could be interpreted as a weakness of the general theory.

Another reason justifying the present test of multiple operational definitions of premorbid reserve is the limitation of traditional definitions of reserve, e.g., IQ and educational level. These definitions can be criticized, for example, as overly-descriptive and non-causal. Also, in many studies, they are confounded with the variable used to measure disease outcome, which is often another neuropsychological or achievement test (Tuokko et al., 2003). In addition, IQ and educational level overlap with other, more distal factors with greater relevance to genetic endowment. In recognition of these limitations, BR was defined in this study by one of the traditional metrics—verbal IQ--in the first set of analyses and by a metric--the presence/absence of paternal alcohol or drug dependence--more relevant to genetic risk for diminished cognitive function, but not independent of the traditional metrics (Finn and Hall, 2004; McIntosh et al., 2005), in the second analysis set.

A fair comparison of the 3 alternate versions of BR theory, and of 2 operational definitions of BR, requires an outcome variable which is continuous and linear over a broad range. For this reason, the P300 event related brain potential was chosen. P300 is a positive-going change in the electroencephalogram which occurs approximately 300−500 msec after the presentation of a stimulus that is novel or otherwise salient, e.g., attended. It has been defined as reflecting the activation of a limited capacity attentional system related to both orienting and working memory (Lefevre at al., 2005; Linden, 2005; Nieuwenhuis et al., 2005; Polich, 2004).

Several reasons justify the choice of P300 as the outcome variable. First, P300 shows remarkable measurement sensitivity over a broad range (Polich, 1998; Polich, 2004; Polich and Herbst, 2000) with excellent, $r \cong 0.8$, test-retest reliability (Williams et al., 2005). Accordingly, it is ideal for testing interactions between factors and minimizing spurious findings which originate from ceiling or floor effects. Second, P300 reflects global functional capacity. Its generators involve circuits within both frontal and nonfrontal regions (Linden, 2005; Ardekani et al., 2002; Bledowski et al., 2004; Clark et al., 2000; Kiehl et al., 2005) and its amplitude and latency are correlated with other measures of global capacity, including IQ (Hansell et al., 2005). Accordingly, it is an appropriate metric for detecting individual differences in brain reserve. Third, the P300 has a long history of value for detecting the effects of HIV/AIDS (Bauer and Shanley, 2006; Polich and Basho, 2002; Polich et al., 2000; Syndulko et al., 1994) and familial substance dependence (Begleiter et al., 1984; Viana-Wackerman et al., 2007; Hesselbrock et al., 2001; Polich et al., 1994; Porjesz et al., 2005). Indeed, the literatures documenting decrements in P300 amplitude, or delays in P300 latency, associated with a family history of substance dependence or a personal history of HIV/AIDS are remarkably consistent.

2. Methods

2.1 Participants and Screening Procedures

One-hundred-fifteen HIV-1 seropositive participants were recruited via advertisements posted within outpatient Infectious Disease Clinics in the greater Hartford, CT region. Interested individuals were invited to telephone a member of the research staff for eligibility screening. The telephone interview included questions about demographic characteristics, general medical status, substance use, and psychiatric symptoms. Individuals who passed the initial telephone screen were invited to visit the Health Center on a subsequent day, during which an IRB-approved consent form and a medical records release were signed. Additional eligibility screening and laboratory evaluations were performed on that day.

The most common method for recruiting the 70 members of the HIV-1 seronegative group was word-of-mouth advertising provided by the seropositive participants. HIV-1 seronegative volunteers were invited to telephone the research assistant for initial screening and were brought to the Health Center for further screening. They were subject to the same protocol as the HIV/AIDS patients.

After completing the informed consent and medical release documents, all participants were asked to provide a blood sample for laboratory confirmation of HIV serostatus. The clinical laboratory evaluation also included CBC with differential, HIV RNA viral load, CD4 lymphocyte count and percent, VDRL, HBV screen, HCV, toxoplasmosis and cytomegalovirus antibody titers, renal and liver function, serum protein, albumin, and G-6-PD. Toxicological analyses for cocaine, opiates, amphetamine, and marijuana were performed on urine samples (Ontrak™, Varian Inc., Palo Alto, CA) and a breathalyzer was used to detect recent alcohol use. In addition, an Optec 2000 Vision Tester™ was used to confirm normal color vision and acuity (with correction).

A structured psychiatric interview, viz., the CDIS-IV (American Psychiatric Association, 1994; Robins et al., 2002), used for detecting DSM-IV Axis I and II disorders, was then administered by a research assistant formally trained in its administration and with 11 years of relevant experience. Participants also completed questionnaires or brief interviews assessing medical history, medication use, parental psychopathology, demographics, psychiatric symptoms, alcohol and drug use, and cognitive status. The assessments included the Addiction Severity Index (ASI; McLellan et al., 1980), Michigan Alcoholism Screening Test (MAST; Selzer, 1971), Drug Abuse Screening Test (DAST-10; Skinner, 1982), and Beck Depression Inventory Version II (BDI-II; Beck et al., 1996). In addition, the Kaufman Brief Intelligence Test (KBIT; Kaufman and Kaufman, 1990) was administered to derive an estimate of VIQ.

Exclusion criteria included pregnancy, seizures, mental retardation, neurosurgery, and a history of head injury with loss of consciousness for greater than 10 minutes. In addition, participants were required to have no acute illness, an IQ score greater than 70, and no major neurological, psychiatric (i.e., DSM-IV-defined schizophrenia or bipolar disorder) or medical (i.e., hypertension, chronic obstructive pulmonary disease, Type 1 diabetes, cirrhosis, hepatic encephalopathy, ocular disorders, etc.) disorders unrelated to HIV/AIDS. Positive urine toxicology or breathalyzer tests or recent (past year) dependence upon alcohol, cocaine, or opiates were also exclusionary. However, current use of methadone was not.

For the analysis, HIV-1 seropositive and seronegative participants were assigned to one of two subgroups defined by a split (< 90 vs. ≥ 90) on the median verbal IQ score for the entire sample. In addition, they were further stratified by the presence (FH^+) versus absence (FH^-) of a report during the interview that the biological father had been diagnosed or treated for an alcohol, cocaine, or opioid use disorder. It would have been preferable to conduct direct interviews with parents to verify the presence versus absence of substance dependence. But, the majority of these participants (mean age = 39 yrs) were unable or unwilling to involve their parents in the study.

2.2 Data Collection

Tin EEG electrodes were applied to 31 scalp sites positioned by an electrode cap (ElectroCap International, Eaton, Ohio). A reference electrode was taped over the bridge of the nose. The ground electrode was applied to the middle of the forehead. Interelectrode impedance was maintained below 5 Kilohms.

After electrode application was complete, the participant was escorted into a sound-shielded chamber and seated in a comfortable chair. The chair faced a 14-inch computer monitor used for the presentation of visual stimuli. A set of shielded stereo headphones, used for auditory stimulus presentation, and other devices (response keys), were located in the immediate proximity of the chair.

Participants performed a discreet trials version (Duncan-Johnson and Kopell, 1981; Bauer and Hesselbrock, 1999) of the Stroop Test (MacLeod, 1991; Stroop, 1935, van Venn and Carter, 2005) in which the stimuli, i.e., the words RED, BLUE, or TOWN, were presented in a red or blue font on the computer monitor. The 6 combinations of words and font colors could later be reduced to three types of trials. These were: (1) compatible font color-word combinations (e.g., the word “BLUE” displayed in blue font), incompatible color-word combinations (e.g., the word “BLUE” displayed in red font), and unrelated (e.g., the word “TOWN” displayed in blue font) combinations.

Three hundred word stimuli were presented with equal probability at a rate of one stimulus every 2.3 seconds for 200 msec each. Participants were asked to indicate the color of the font

by pressing one of two response keys within a response deadline of 1500 msec. They were also asked to ignore the word.

The electroencephalogram was recorded throughout the task. For the detection of eyeblink and eye movement artifacts, a pair of electrodes were placed diagonally above and below the left eye. The 31 channels of the EEG and 1 channel of eye movement (EOG) activity were appropriately amplified (EEG gain=20K, EOG gain=2K) and filtered (bandpass=0.01−12 Hz) using a SA Instrumentation Company amplification system. Along with markers indicating stimulus and response onsets, the EEG and EOG channels were routed to an A/D converter, and sampled at a rate of 200 Hz for 50 msec preceding and 950 msec following the onset of each stimulus. During off-line computations, single trial data were sorted by electrode and trial type. Before averaging, trials containing an eye movement deviation greater than 50 μV were deleted. Trials with A/D converter overflow and incorrect responses were also deleted.

Time-point averaged waveforms were then created from a minimum of 20 accepted trials of each of the compatible and incompatible types. P300 was estimated by the summated area under the curve between 250 and 500 msec following stimulus onset. This area measure was chosen over a peak amplitude measure because a distinct peak was not consistently present in the records of all 185 subjects under both trial conditions. The interval of 250−500 msec was chosen because it is a time period proximal to the discrimination of the stimuli and the execution of the motor response.

Behavioral performance indices were also recorded during the task and summarized off-line. Average reaction time and the percentage of trials with correct responses were sorted by incompatible and compatible trial types and preserved for analysis.

2.3 Data Analysis

The 8 groups of subjects were initially compared on background characteristics. Pearson's Chi-Square Test evaluated group equivalence on categorical variables. A three factor ANOVA served the same purpose for continuous variables. Significant interaction effects revealed by ANOVA were further evaluated with Tukey post hoc tests.

Behavioral performance was analyzed for each major design. Reaction time and response accuracy were analyzed separately via repeated measures ANOVA with trial type (compatible, incompatible) as a within-subjects factor, and the three grouping factors.

In an attempt to reduce the number of analyses on P300 area, and the attendant risk of Type I error, a factor analysis was performed on P300 area across the 31 electrode sites. The goal was to find topographic regions of homogeneity which could be reduced to a single score. A principal components analysis followed by varimax rotation yielded two factors which explained most of the variance across the 31 sites. The frontal sites exhibited greater loadings on the first factor. The sites around and posterior to the central sulcus exhibited greater loadings on the second factor. Highly similar factor structures were obtained for both incompatible and compatible trial data. We therefore chose to calculate average area scores representing P300 amplitude within anterior (FP1, FP2, AF1, AF2, F3, F4, F5, F7, FZ, FC2, FC4, FC5, FC6) and posterior (C3, C4, CZ, CP1, CP2, CP5, CP6, P3, P4, PZ, T7, T8, P7, P8, PO1, PO2, O1, O2) regions. These scores were analyzed via repeated measures ANOVAs with HIV/AIDS, VIQ, and FH as grouping factors, and trial type and scalp region as repeated measures factors.

Of principal interest in the P300 analyses was the pattern of relationship between either FH and VIQ (as putative indices of brain reserve) and HIV/AIDS. As we show in Figure 1a, a simple additive relationship between HIV/AIDS and brain reserve would be indicated by significant main effects of each with no significant interaction. However, a significant

interaction could indicate either a synergistic (Figure 1b) or underadditive (Figure 1c) relationship. The latter pattern was hypothesized.

3. Results

3.1 Background Characteristics

The participants included in the analyses can be broadly characterized as men and women of various racial/ethnic origins, approximately 39 years of age, educated for an average of 11.85 years, and possessing either no or mild symptoms of depression. Many had histories of illicit drug abuse and/or alcohol abuse; however, DSM-IV-defined dependence on illicit drugs or alcohol during the year prior to the P300 assessment was exclusionary. The HIV-1 seropositive participants were remarkably healthy: viral loads were low and CD4+ T-lymphocyte counts were, in the typical case, greater than 200 cells/μl. Table 1 summarizes the demographic, substance use, psychological, and medical characteristics of these participants as a function of their verbal IQ rank relative to the median (< vs. ≥ 90), FH, and HIV-1 serostatus.

The groups differed on few characteristics. Some differences were expected because they are related to group assignment. For example, the low and high verbal VIQ groups differed significantly on years of education by an average of 1.7 yrs [$F(1,177)=33.3$, $p<0.001$]. And, the FH^+ group reported an average of 2.2 more alcohol problems on the MAST than the FH^- group [$F(1,177)=5.1$, $p<0.02$]. The HIV^+ and HIV^-groups differed on CD4 cell count [$F(1,177)=105.2$, $p<0.001$].

Some unexpected but small differences occurred for other demographic characteristics. A lower versus higher VIQ was associated a minor but statistically significant 3.2 unit decrease in depression symptoms on the BDI-II [$F(1,177)=12.9$, $p<0.001$]. In addition, HIV^+ subjects were, on average, 3 yrs older than their HIV^- peers [$F(1,177)=7.7$, $p<0.006$]. There were no significant interactions involving the grouping factors.

3.2 Task Performance Results

The analysis of reaction time revealed a significant effect of trial type [$F(1,177)=161.6$, $p<0.001$]. It was greater when the irrelevant stimulus word and relevant stimulus font cued incompatible responses than when they cued the same response. Family history modified the effects of trial type on reaction time [$F(1,177)=9.0$, $p<0.003$]: the reaction time difference between incompatible and compatible trials, i.e., the Stroop effect, was significantly greater in the FH^+ [incompatible trial (M ± SD): 0.63 ± .13; compatible trial: 0.57 ± .13] than FH^- (incompatible: 0.57 ± .12; compatible: 0.53 ± .11) groups. The magnitude of the Stroop effect did not vary by VIQ [trial type × VIQ: $F(1,177)=0.01$, $p=0.92$] or HIV [trial type × HIV: $F(1,177)=0.09$, $p=0.77$].

The analysis of reaction time yielded several other significant effects. Generally, subjects with a positive family history [0.61 ± .15 vs. 0.54 ± .11; $F(1,177)=10.5$, $p<0.001$], or a lower VIQ [0.61 ± .12 vs. 0.54 ± .14; $F(1,177)=12.5$, $p<0.001$], were slower to respond than their FH^- or higher VIQ peers. FH also modified the effects of HIV/AIDS on reaction time [$F(1,177)=5.4$, $p<0.02$] whereas VIQ had no such effect [$F(1,177)=1.9$, $p=0.16$]. Unfortunately, the interaction between FH and HIV/AIDS is not readily interpreted. The absence versus presence of HIV/AIDS was associated with a reaction time increase of .042 sec among FH^- subjects. But, among FH^+ subjects, HIV/AIDS was associated with .053 sec change in the opposite direction. No other main or interaction effects were significant.

The analysis of performance accuracy yielded an interaction between trial type and FH [$F(1,177)=4.7$, $P<0.03$] which was consistent with the interaction found for reaction time: the magnitude of the Stroop effect was greater in the FH^+ (incompatible: 95.1 ± 7 %; compatible:

97.3 ± 6 %) than FH^- (incompatible: 95.6 ± 8 %; compatible: 96.6 ± 7 %) groups. As in the analysis of reaction time, there was also a significant main effect of VIQ [$F(1,177)=5.4$, $p<0.02$]. Increased VIQ was associated with an increase in response accuracy from 95.0 ± 6 % to 97.5 ± 6 %. VIQ was again not associated with a change in the magnitude of the Stroop effect. It also did not interact with HIV.

3.3 P300 Results (Figure 2)

The analysis yielded no significant effects involving VIQ as a factor. Yet, it did yield several significant effects involving FH and HIV/AIDS. For example, the interaction of FH and HIV/AIDS was significant [$F(1,177)=3.7$, $p<0.05$]. Tukey post hoc tests revealed a decrement in P300 area associated HIV/AIDS (HIV^- = 3497 ± 2774; HIV^+ = 2136 ± 2049) in the FH^- group. In the FH^+ group, HIV/AIDS was associated with no significant change in P300 (HIV^- = 2088 ± 4622 vs. HIV^+ = 2331 ± 3471). This interaction is illustrated in Figure 3 and is consistent with the prediction of the underadditive model shown in Figure 1c.

HIV was also associated with an overall reduction in P300, but only over the anterior scalp region [HIV × Region: $F(1,177)=9.8$, $p<0.002$]. The magnitude of the HIV effect was ⁻920 uV over the anterior region and ⁻197 uV over the posterior region. The 2-way interaction of HIV and Region was qualified by a complex 4-way interaction that also included trial type and FH [$F(1,177)=4.4$, $p<0.03$]. An examination of the means illustrated in Figure 4 indicates that P300 was generally larger on compatible than incompatible trials. This difference was more pronounced at anterior versus posterior electrodes among subjects with no FH and without HIV/AIDS. Thus, in contrast to the findings from the analysis of reaction time, the analysis of P300 showed a reduced Stroop effect associated with FH and HIV/AIDS.

4. Discussion

The present study was designed to test the relative validity of three versions of brain reserve theory within an ethnically-diverse sample of men and women living with HIV/AIDS. It also contrasted the effects of two alternate operational definitions of the construct for the purpose of evaluating the generality of the theory. The analyses revealed three major findings: (1) In contrast to the predictions of the most popular version of brain reserve theory (Figure 1b), high VIQ did not moderate the adverse effects of HIV/AIDS nor did low VIQ potentiate these effects; (2) HIV/AIDS and a family history of substance abuse or dependence both reduced P300 area over the frontal scalp; (3) The effects of HIV/AIDS on frontal P300 area were blunted among subjects with a positive FH (Figures 1c and 3). The latter finding is consistent with the underadditive version of BR theory illustrated in Figure 1c and inconsistent with the additive and synergistic versions illustrated in Figures 1a and 1b..

Since its initial proposal (Katzman et al., 1988), reserve theory has been subject to several challenges and criticisms. One criticism is the manner in which the reserve construct has been defined. In many HIV studies (Stern et al., 1996; Pereda et al., 2000), either VIQ, educational attainment, or occupational attainment is the definition of convenience. In such studies, the definition is a proxy for an assemblage of unmeasured factors which may or may not be relevant to the structural or functional capacity of the brain. For example, HIV/AIDS patients with higher intelligence or attainment may simply be more motivated, or more experienced with tests, than their less intelligent or accomplished peers and would accordingly perform better on any outcome test of cognitive function or achievement. To avoid this ascertainment bias (Tuokko et al., 2003) in the present study, we employed an outcome test less affected by motivation and familiarity.

HIV/AIDS patients with higher VIQ or attainment may also be more likely to seek health care services (Cunningham et al., 2005). As a result, the HIV/AIDS diagnosis may occur at an earlier

stage of the disease allowing early initiation of treatment. Or, patients with higher VIQ or attainment may be more compliant with treatment (Borrell et al., 2006). In both instances, patients with superior "reserve" may accordingly experience a less severe course of the disease resulting in less impairment. It is important to note that this confound is less of a concern for the present study because the low (IQ<90 or FH^+) and high (IQ≥90 or FH^-) reserve groups did not differ on current measures of illness severity, including CD4 count and viral burden. Admittedly, current illness severity might not the ideal variable on which to evaluate group equivalence. The nadir CD4 count during a patient's lifetime may be a better predictor of his/her current cognitive or neurological status (Valcour et al., 2006).

A third potential problem for the extant theoretical models is the questionable hypothesis of synergistic interaction of reduced premorbid reserve and HIV/AIDS. Whether low brain reserve reduces (Figure 3), enhances (Stern et al., 1996), or is independent of, the deleterious effects of HIV/AIDS may depend critically upon the degree of neuroanatomical and functional overlap of HIV/AIDS with the chosen operational definition of reserve as well as their relationships with the outcome measure. The present results suggest greater overlap in the effects of HIV/AIDS with one definition of reserve, viz., FH, insofar as both affected P300, whereas the other definition, viz., VIQ, did not. Hence, an interaction between HIV/AIDS and FH was more probable.

One should exercise caution in interpreting these results. For example, it is possible that the degree to which HIV/AIDS interacts with one versus another definition of reserve is dependent upon the association between the definition and the context (i.e., the cognitive task) within which disease outcome is evaluated. For this study, we chose the Stroop task because it has repeatedly been shown sensitive to the effects of FH (e.g., Lovallo et al., 2006) and HIV/AIDS (Martin et al., 2004). VIQ, in contrast, appears to be more strongly correlated with working memory than with performance on the Stroop task or similar tasks measuring cognitive control (Boone et al., 1998).

A second important caveat is the possibility that the effects of FH are explained by a confounded difference between the FH^+ and FH^- groups in their personal histories. Mediation by drug use, or depression severity, appears unlikely because the groups did not differ significantly on these variables. Furthermore, a past year history of alcohol or drug dependence was exclusionary. Yet, the groups did differ significantly on the MAST, which measures the lifetime number of alcohol problems. Specifying MAST scores as a covariate did not affect the results.

A more likely confound is Antisocial Personality Disorder which we (Bauer and Shanley, 2006) and other groups (see Bauer & Houston, 2004, for a review) have described as an important mediator of the effects of FH on P300. In fact, the association is of such a magnitude that statistically controlling for the effects of conduct problems will typically eliminate the effects of FH on P300 (e.g., Bauer and Hesselbrock, 1999; Viana-Wackerman et al., 2007).

The present demonstration of similar effects of HIV/AIDS and FH on frontal P300 area is consistent with other reports documenting susceptibility of the frontal brain to HIV-1 (Bauer and Shanley, 2006; Chang et al., 2003; Cloak et al., 2004; Wu et al., 2006), a family history of alcoholism (Bauer and Hesselbrock, 2002; Schweinsburg et al, 2004), and attendant factors--e.g., Conduct Disorder/Antisocial Personality Disorder (Bauer and Houston, 2004; Bauer and Shanley, 2006; Bauer and Hesselbrock, 2001; Hoptman, 2003; Nakano et al., 2006; Raine et al., 2000; Yang et al., 2005)--which increase the risk for both HIV/AIDS (e.g., Brooner et al., 1993; Erbelding et al., 2004) and substance abuse/dependence (e.g., Hesselbrock et al., 1985; McGovern et al., 2006). The demonstration of an interaction between HIV/AIDS and FH also raises interesting questions regarding genetic vulnerability to neurocognitive impairment in HIV/AIDS. Admittedly, family history is not an ideal independent variable for testing genetic

hypotheses because it captures both genetic and environmental effects. An investigation of candidate genes could be fruitful.

One possibility for investigation is the COMT gene, for polymorphisms of this gene have been shown to alter both P300 (Gallinat et al., 2003) and the performance of neurocognitive tasks, e.g., Stroop (Reuter et al., 2005), which reflect frontal brain function. A second possibility is the GABRA2 gene on chromosome 4. GABRA2 is likely related to neurocognitive impairment in HIV/AIDS via it association with intermediate risk factors, including conduct problems (Dick et al., 2006) and alcohol (Edenberg et al., 2004; Lappalainen et al., 2005; Covault et al., 2004) and other drug (Agrawal et al., 2006; Dick et al., 2006) dependence. It has also been linked to an excess of high frequency (fast beta) electroencephalographic power (Edenberg et al., 2004) generated within the same frontal brain regions (Bauer and Hesselbrock, 2002; Isotani et al., 2001; Kondakor et al., 1997) where HIV/AIDS exerts significant effects (Bauer and Shanley, 2006; Chang et al., 2003; Cloak et al., 2004; Wu et al., 2006).

It is important to not conclude from these findings that a FH of substance abuse/dependence will blunt all of the neurological effects of HIV/AIDS or the P300 changes associated with severe disease, i.e., dementia. The HIV-1 seropositive patients enrolled in this study were generally healthy and without acute illness. Our findings can only be generalized to this subpopulation. Yet, in the current era of effective antiretroviral therapies--during which acute illness, dementia, and frailty are less common--the relative contributions of family history and coexisting psychiatric disorders to functional impairment in HIV/AIDS are greater and therefore warrant increased attention.

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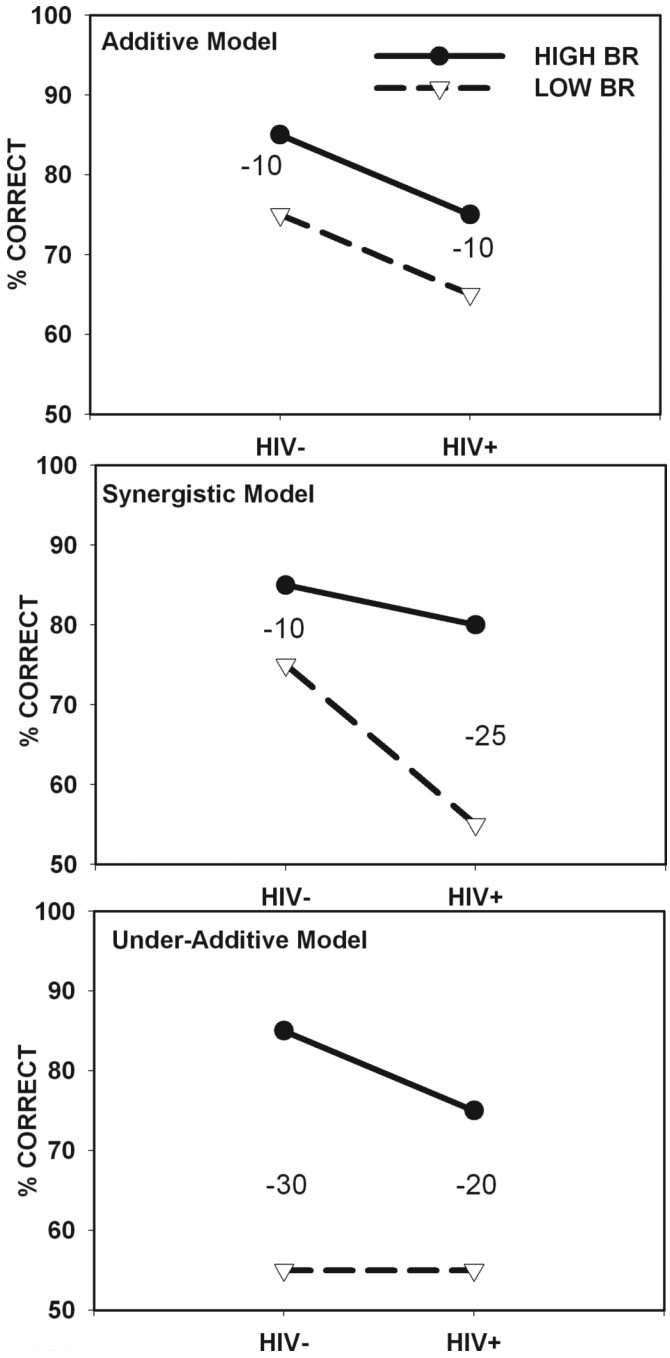

Figure 1a,b,c.
Alternate versions of brain reserve (BR) theory.

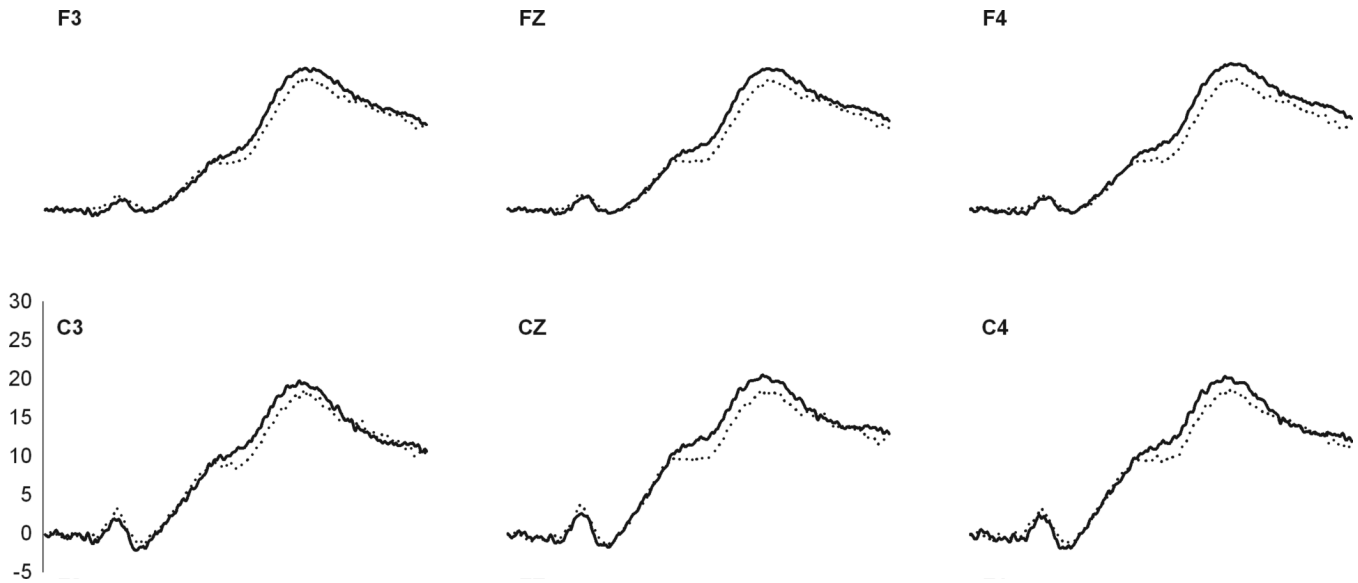

Figure 2.

ERP waveforms averaged within the FH-, HIV- group depicting the effects of trial type on P300 area across 9 representative electrode sites. Area was calculated between the dashed vertical lines ranges from 250 to 500 msec post-stimulus onset (designated by arrow). Each tic mark on the x-axis represents 100 msec.

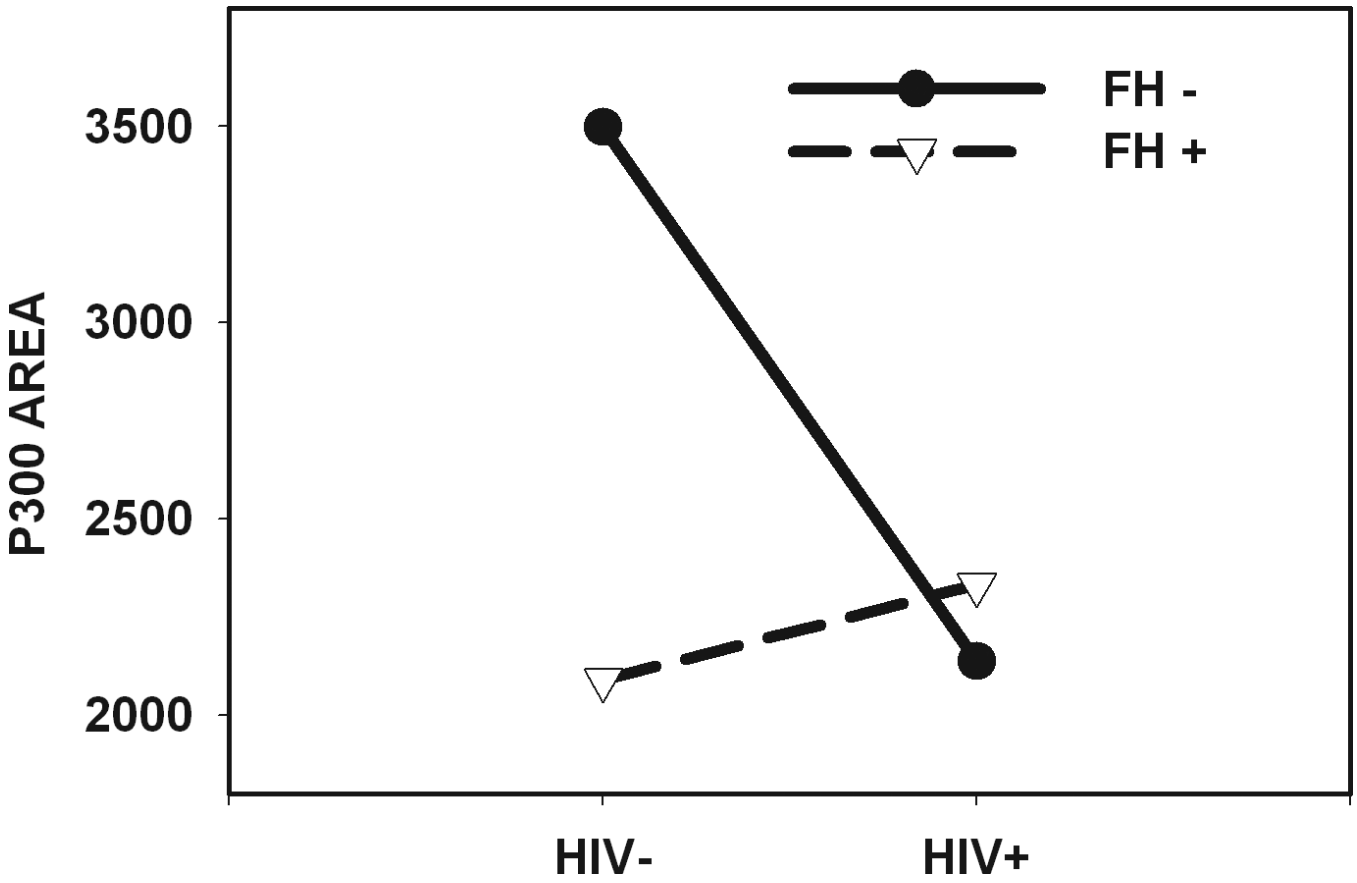

Figure 3.
Effects of HIV-1 serostatus and a family history of substance abuse or dependence on P300 area. Note the similarity of this relationship to the under-additive theoretical model illustrated in Figure 1C.

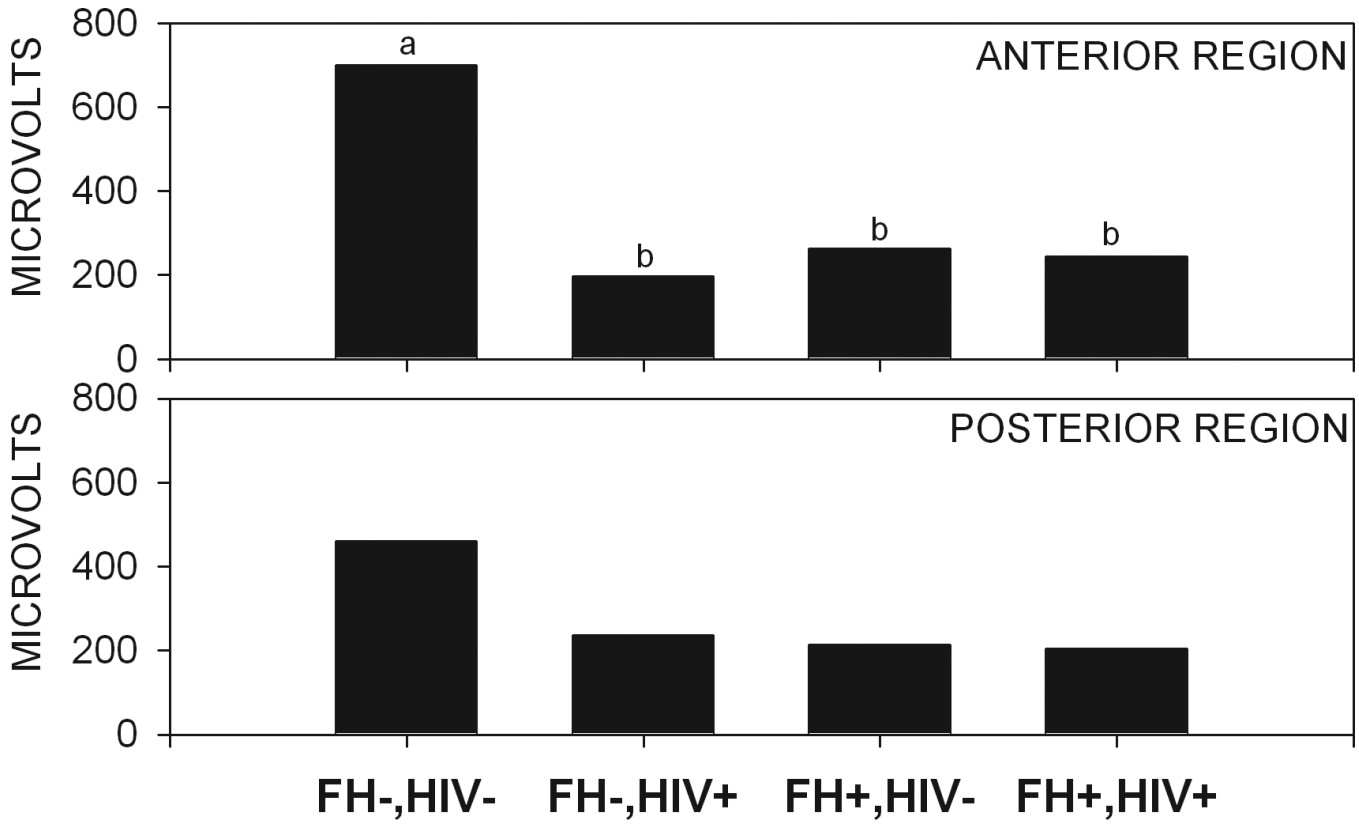

Figure 4.
Difference in P300 area between compatible and incompatible trials as a function of group and region. Mean values labelled “a” and “b” are significantly different.

Table 1

Background Characteristics of the 8 groups. Columns with different subscripts are significantly different ($p<0.05$).

Characteristic	**HIV- FH- VIQ<90 N = 18**	**HIV- FH- VIQ≥90 N = 9**	**HIV- FH+ VIQ<90 N = 22**	**HIV- FH+ VIQ≥90 N = 21**	**HIV+ FH- VIQ<90 N = 28**	**HIV+ FH- VIQ≥90 N = 22**	**HIV+ FH+ VIQ<90 N = 26**	**HIV+ FH+ VIQ≥90 N = 39**
Age, mean (SD), y	35.2(5.2)	38.0(8.2)	37.8(8.8)	37.7(7.5)	40.0(6.0)	42.2(6.6)	38.2(6.1)	40.5(6.3)
Male, %	61.1	44.4	31.8	47.6	50	63.6	46.2	59
Education, mean (SD), y	$10.6(1.7)_a$	$13.6(2.5)_b$	$11.5(1.5)_a$	$12.5(1.7)_b$	$11.3(1.9)_a$	$12.2(1.7)_b$	$10.7(1.4)_a$	$12.6(2.1)_b$
MAST Score, mean (SD)	$2.7(4.1)_a$	$3.3(6.3)_a$	$4.0(5.5)_b$	$4.5(5.8)_b$	$3.3(5.3)_a$	$3.8(5.6)_a$	$7.6(6.4)_b$	$5.7(7.0)_b$
DAST-10 Score, mean (SD)	3.7(2.9)	1.8(2.6)	3.5(2.6)	3.7(3.3)	2.5(2.8)	2.7(3.5)	4.3(3.2)	3.5(3.9)
BDI-II Score, mean (SD)	13.1(9.6)	10.4(5.8)	16.1(9.5)	12.1(10.4)	18.7(14.8)	9.5(5.6)	20.3(12.1)	12.2(8.6)
Methadone Maintenance, %	37.5	25	16.7	25	22.2	9.1	4.0	18.4
CD4 count, mean (SD), cells/μL	$814(195)_a$	$816(323)_a$	$1055(442)_a$	$903(318)_a$	$404(328)_b$	$352(186)_b$	$370(223)_b$	$416(332)_b$
Log_{10} Viral Load, mean (SD)	--	--	--	--	0.69(0.91)	1.02(0.89)	0.84(1.03)	1.28(0.96)
AIDS, %	--	--	--	--	32.1	27.3	23.1	28.2
Antiretroviral treatment, %	--	--	--	--	75	68.2	50	66.7